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A New Way to Classify Genetic Skin Disease

Celia Moss[1]

Genetic disorders with skin manifestations often affect other organs as well, and diseases with a similar array of features might be linked pathogenetically. Classifying disorders by individual phenotypic components may reveal clusters with a common genetic cause and elucidate pathogenic links. If components are categorized inadequately, however, the method will simply confirm what is known, obscure true links, and suggest false ones.

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In this issue, Feramisco and colleagues identify 688 genetic skin disorders with both a characteristic cutaneous phenotype and a distinct molecular basis. The number of known genodermatoses has risen linearly since 1991, when about 90 such disorders were cataloged (Moss, 1991), through 2006, when we tabulated 580 such diseases (Leech and Moss, 2007). As the number of known genodermatoses increases, it becomes both more necessary and more rewarding to organize this information. Clinicians want catalogs they can search for a diagnosis; biologists need precise clinical descriptors to make sense of molecular information; and new patterns emerge as we arrange the mosaic fragments. Feramisco and colleagues present a system of describing genodermatoses in terms of their individual cutaneous and systemic features in order to explore their relationships with one another and with genes and molecular pathways.

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Nosology of skin disease

Dermatologists have long sought to classify skin disorders. In the eighteenth and early nineteenth centuries, Joseph Plenck of Vienna, the Edinburgh physicians Robert Willan and Thomas Bateman, the Parisian Louis Marc Alibert, and the American Noah Worcester categorized dermatoses according to lesion type, inspired by the Linnaean system for plants (Connor, 2004). By the mid-nineteenth century, a better understanding of etiology facilitated pathological classification, led by Ferdinand Hebra of Vienna, and this is reflected in the chapter headings of many standard dermatology textbooks. Meanwhile, politicians and reformers were also taking an interest in nosology; the first International List of Causes of Death, issued in 1900, was the forerunner of the 1989 International Classification of Diseases (ICD10), which is still in use (see "Web Resources"). Detailed though it is, the ICD10 does not meet the needs of dermatologists, and the British Association of Dermatologists has developed its own comprehensive diagnostic and procedural dictionaries with a clinically logical hierarchy of terms, more detailed than, but still mapped to, the ICD10 (see "Web Resources").

Feramisco *et al.* (2009, this issue) use the classification and disease descriptions of the geneticist Victor McKusick (1921–2008), who in 1966 published the first catalog of known genetic traits, *Mendelian Inheritance in Man*; 40 years later, he was still contributing to the online version, OMIM (see "Web Resources"). The distinctive tomes can still be seen on dermatologists' bookshelves; for me, the silver ninth edition was a significant acquisition. McKusick's classification is admirably simple: a broad split by mode of inheritance and, within that, alphabetical listings. The clinical features are described succinctly and authoritatively, together with genes and allelic variants. OMIM is part of the National Center for Biotechnology Information Entrez system, which provides a massive information base, linking, for example, clinical descriptions (OMIM) with genes, proteins,

and biosystems (pathways and systems of interacting molecules). Dr McKusick died in 2008.

> Clustering by phenotype may help identify disorders and genes for future study.

Describing phenotypes

Feramisco *et al.* identified 826 OMIM disease entries with both skin manifestations and a defined genotype. They excluded 138 with "undesignated" cutaneous phenotypes, leaving 688 "disease units" (i.e., diseases with a distinct genotype), separately listing phenocopies representing genetic heterogeneity. For later analysis they reduced the number to 560 by counting such phenocopies only once. They tabulated the 688 disease units alphabetically, with OMIM numbers, gene, and locus, in a manner similar to that of Leech and Moss (2007). They then broke down the phenotypes of these disorders into 1,640 cutaneous and 2,551 extracutaneous features using the clinical entries in OMIM—a reasonably straightforward, if laborious, process. The next stage was necessary but more subjective: reducing the number of parameters by merging features into groups. The cutaneous categories are in some cases anatomical (e.g., hair/nails), whereas in others they are morphological (e.g., blistering) or pathological (e.g., autoimmune), so the categories are not mutually exclusive. Some skin categories are broad—for example, "nails" includes everything from anonychia to pachyonychia and onychogryposis; some are narrow (e.g., "hypo/anhidrosis"). Systemic categories are mostly defined by organ and are necessarily much broader. Cutaneous phenotypes were thus categorized into 18 numbered groups with alphabetical subgroups and extracutaneous features into 17 alphabetical groups (cleverly using the initial letter of the organ system) with numbered subgroups. So type 1 Waardenburg syndrome becomes 2C, 11C; A, D1, U, signifying hypopigmentation and change in hair and auditory, dysmorphism, and urogenital anomalies. Junctional epidermolysis bullosa with pyloric atresia becomes 4B, 6,16,11D,17;G1,G2,U, signifying skin aplasia/fragility, blistering, mucosal and nail involvement and congenital malformation of the gut, other gut involvement, and urogenital anomaly. The catalog is named "CGenDerm" and is presented as an Excel spreadsheet.

The selection of categories was no doubt difficult, and the authors provide no information about how it was carried out. Some allocations are surprising. For example, teeth are considered systemic rather than cutaneous and are not included in the description of hypohidrotic ectodermal dysplasia. The authors chose to divide the cornifying disorders into 1A xerosis, 1B hyperkeratosis not otherwise specified, 1C hyperkeratosis acanthosis type, and 1D hyperkeratosis ichthyosis/scaling type. Where does that leave the palmoplantar keratodermas? 1B apparently. Darier's disease is also allocated to 1B and also, curiously, to 10 (immune mediated). It seems possible that the choice of category might have been informed consciously or unconsciously by a knowledge of genotype: the palmoplantar keratodermas are clinically distinct but genetically diverse, and transmembrane signaling may emerge as a theme among the 1B group.

Feramisco *et al.* (2009) refer to the process of categorizing individual disease features as "phenotype deconvolution." A similar approach was used 25 years ago by Freire-Maia and Pinheiro (1984), who classified 117 ectodermal dysplasias according to whether they affected hair (1), teeth (2), nails (3), or sweat glands (4). To some extent, the same process has been used in clinical terms, such as odonto-tricho-ungual-digital-palmar and LEOPARD syndromes. Although this may be a rational alternative to naming diseases after a particular organ, feature, physician, or patient, clinicians generally prefer a simpler, if more limited, term. Although still widely cited, the 1-2-3-4 nomenclature never caught on among clinicians, and it is difficult to imagine the approach of Feramisco *et al.* doing so either. However, the "bottom-up" approach of searching for diagnoses on individual clinical features is highly effective and widely used, for example, in *Smith's Recognizable Patterns of Human Malformation* (Jones, 2006), the London Medical Databases (see "Web Resources"), and, indeed, OMIM. CGenDerm was designed to enable biologists to interpret clinical data, not to make life easier for clinicians (at least not directly), but it could easily be reformatted to that end.

Clustering by phenotype

The purpose of CGenDerm is to highlight relationships among disorders to guide research. First, the authors used cluster analysis based on the presence or absence of individual cutaneous and systemic features. For example, diseases with café-au-lait macules fall into a central nervous system tumor cluster (e.g., neuroblastoma and neurofibromatosis type 2), a chromosomal instability cluster (e.g., Bloom's syndrome, Fanconi's syndrome, and ataxia telangiectasia), and an NF1 cluster (neurofibromatosis type 1 and Watson's syndrome). For laboratories interested in a particular gene or pathway, this might identify other candidate disorders, and it would be interesting to include genodermatoses for which the pathogenesis is currently unknown. The ectodermal dysplasias might also be analyzed in this way, using the 1-2-3-4 classification. The subjective allocation of features to categories and the degree of subclassification might, however, prejudge the findings and produce "red herrings." It is not surprising that a skin disease cluster featuring systemic malignancy (Bloom's syndrome, Fanconi's syndrome, and ataxia telangiectasia) exhibits a common pathogenetic feature (chromosomal instability). Conversely, the analysis unexpectedly clusters McCune–Albright and Rubinstein–Taybi syndromes on the basis that both have café-au-lait macules and auditory, skeletal, and ocular abnormalities; the disparate systemic features of the two disorders are masked by the broad systemic groupings, and the link might not be real. The same applies to Fanconi's syndrome and LEOPARD syndrome, linked by sharing hyperpigmentation, café-au-lait macules, deafness, abnormal growth, and neurological and musculoskeletal disorders, the last three of which are particularly broad groups. CGenDerm must be vindicated by elucidating new pathogenetic links and testing prospectively with "orphan" diseases—those whose genetic basis is unknown.

Clustering by gene

The authors examined 501 genes responsible for the 560 genodermatoses defined by a unique OMIM entry. The mismatch is attributable to the possibility that a single gene can cause more than one disease (allelic variants and pleiotropy) and, conversely, a single disease can be caused by different genes (phenocopies and genetic heterogeneity). Genes operate within intricate pathways and networks, many of which are known. The authors use existing software to map these 501 genes onto these known networks, highlighting nodes and groups of disorders. This exercise does not take into account variation caused by type of mutation, let alone epigenetic factors. Nonetheless, the authors demonstrate overlapping networks of genes—for example, those causing depigmentation, deafness, or both—and this process will undoubtedly reveal new candidate genes for disorders of unknown cause. This type of analysis could be applied to the 1-2-3-4 ectodermal dysplasia classification now that several ectodermal dysplasia genes and pathways are known.

Where does this take us?

Despite some intrinsic limitations and simplifications, this analytical approach may help researchers identify candidate disorders and genes for future study. CGenDerm can be improved and extended in the future. It might be adapted to form a searchable database to aid clinicians. It remains to be seen whether the analytical methods will tell us more than existing search engines and Sherlockian deduction—a process that works only because the author already knows the answer.

CONFLICT OF INTEREST

The author states no conflict of interest.

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WEB RESOURCES

British Association of Dermatologists: http://www.bad.org.uk/site/920/default.aspx

History of the International Classification of Diseases: http://www.who.int/classifications/icd/en/HistoryOfICD.pdf

National Center for Biotechnology Information Entrez System, National Library of Medicine: http://www.lmdatabases.com/index.html

Online Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/omim

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Stromal Collagenase in Melanoma: A Vascular Connection

Veli-Matti Kähäri[1] and Risto Ala-aho[1]

In this issue, Zigrino *et al.* report on the role of host-derived mouse collagenase-3 (matrix metalloproteinase (MMP)-13) in melanoma growth and metastasis using a mouse model that lacks MMP-13. The authors demonstrate that vascularization of cutaneous melanomas in these mice is impaired compared with that of controls. This study emphasizes the importance of stromal murine MMP-13, a functional homologue of human MMP-1, in tumor progression.

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Proteinases in tumor growth

Tumor progression is a multistage process in which malignant cells invade surrounding tissue and metastasize to distant organs. An important stage of tumor invasion is the loss of an intact basement membrane. Subsequently, malignant cells metastasize to other organs by invading blood or lymphatic vessels. Tumor cells then enter blood or lymph circulation, attach at a distant location, and degrade the basement membranes and extracellular matrix (ECM) at the sites of metastases. Furthermore, angiogenesis is required for tumor growth, and tumor-induced lymphangiogenesis plays an important role in tumor metastasis (Karpanen and Alitalo, 2008).

Collagenases

Collagenase-1 (matrix metalloproteinase (MMP)-1), collagenase-2 (MMP-8), and collagenase-3 (MMP-13) are principal secreted proteinases capable of cleaving native fibrillar collagens of types I, II, III, V, and IX. In addition to MMP-1, MMP-8, and MMP-13, gelatinase-A (MMP-2) has a weak catalytic activity toward fibrillar collagens (Ala-aho and Kähäri, 2005). Furthermore, membrane-type-1 MMP (MMP-14) cleaves fibrillar collagens. Collagenases vary in their ability to catalyze fibrillar collagens.

The first MMP to be identified, a collagenase, was purified from the tails of tadpoles by Gross and Lapière (1962). The first human MMP to be identified, MMP-1, was cloned from adult skin fibroblasts (Goldberg *et al.*, 1986). Human MMP-1 is expressed in physiological processes, for example, during embryonic development and wound healing, as well as under a number of pathological conditions, including chronic cutaneous ulcers and various malignant tumors. MMP-1 is expressed by a variety of normal cells

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